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Cranial Nerve I: Olfaction

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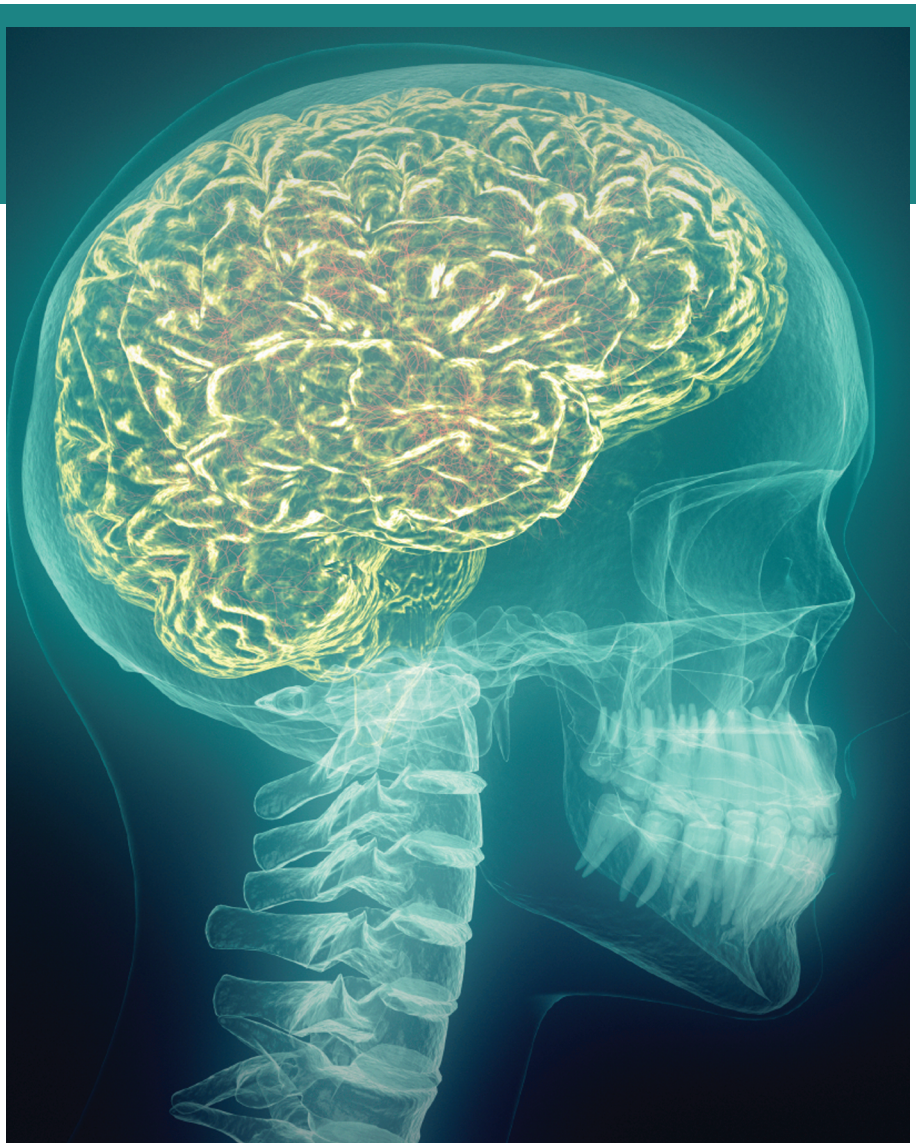
In this series, Dr. Sanders and Dr. Gillig explain how aspects of the neurological examination can aid in differential diagnosis of some common (and some uncommon) disorders seen in psychiatric practice.



ABSTRACT

Olfactory (smell) testing is one of the most interesting and revealing individual neurologic tests in psychiatric research. It is also one of the most neglected tests in the clinical practice of psychiatry. There are several diagnostic applications of smell testing in clinical psychiatry. This review covers reasons for the psychiatrist to test olfaction, ways of testing olfaction, and how to interpret test results.

INTRODUCTION

Cranial nerve testing is particularly useful for detecting and localizing brain pathology, and some of the most interesting and consistent findings in psychiatry involve cranial nerve functioning. Still, the cranial nerves tend to get little attention in the psychiatric clinical examination. There are probably two chief reasons for this: One tends to forget how to administer and interpret these tests, and one tends to forget where to find the test materials (especially those used for sensory testing).

Although it conveys superficial attention to the cranial nerves, the common expression "CN II-XII intact" explicitly snubs the olfactory nerve. There are, of course, reasons for this

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neglect. Olfactory testing requires specific stimuli, which may require a trip to the kitchen or the cafeteria, if not to a more specialized vendor.[1] Still, it is easy to screen for anosmia, and in several situations it is worthwhile. Emerging evidence suggests that olfactory testing can help answer several difficult diagnostic questions in psychiatry.

OLFACTION AS A "FRONTAL LOBE" SIGN

The neurobiology of olfactory sensation and perception is analogous to the other senses.[2,3] Receptor neurons carry information to central processing centers (chiefly medial temporal cortex and amygdala), which relay to association centers (many frontal and limbic structures). Complete loss of the sense (anosmia) reflects damage to the receptors or neurons early in the afferent pathway, while perceptual deficits (e.g., inability to identify or match odors) reflects problems with further afferents or relays.[2] Predictable (reflexive) motor responses, such as sniffing, follow the activation of simple circuits; more complex responses involve multiple neocortical areas. Because the primary olfactory structures adhere to the ventral frontal lobes and connect to limbic circuits, which involve ventromedial frontal cortex, olfactory perception is often considered a frontal lobe sign. This is somewhat simplistic, but largely accurate.[3,4]

SOME COMMON CONDITIONS RESULTING IN OLFACTORY DEFICITS

Olfactory deficits of some sort have been described in rhinitis and sinusitis, normal aging, normal male subjects, cigarette smokers, cognitive disorders (both developmental and degenerative), movement disorders, traumatic brain injury, epilepsy, after various injuries to frontal or temporal lobes, sphenoidal ridge tumors, schizophrenia, anxiety, and depression.

Viewed from this distance, smell testing seems hopelessly nonspecific, but certain tests are very helpful with certain diagnostic questions.

OLFACTORY DEFICITS IN THE GENERAL POPULATION

Women tend to perform better on olfactory tasks than men, and olfactory performance declines, starting at around 60 to 65 years.[5–7]

Rhinitis and sinusitis can prevent the stimulus from reaching the olfactory nerve endings and can disable the receptors. Deficits associated with these illnesses are usually transient. Testing should be deferred until a few weeks after recovery from clinical symptoms to be valid. Occasionally, olfactory function recovers very slowly or not at all. Viral upper respiratory infection is one of the most common causes of persistent anosmia.[8] This may be partly because with such infections may come zinc, probably useful as a cold remedy but also a known olfactory neurotoxin. Vigorous sniffing of Zicam solution (rather than the intended intranasal topical application) seems to have given some persistent anosmia.[9] Curiously, systemic zinc may be helpful in disturbances of taste and smell.[10,11]

Cigarette smoke is a toxin, and smoking is associated in a dose-related fashion with reduced olfactory sensitivity.[12] It recovers gradually after smoking cessation,[13] possibly contributing to the weight gain commonly associated with smoking cessation. The impact of smoking is generally modest, and cannot be blamed for clinical deficits. Clinical applications of smell testing are summarized in Table 1.

NEUROPSYCHIATRIC SIGNIFICANCE OF OLFACTORY DEFICITS: DEMENTIA, PARKINSON'S DISEASE, DEVELOPMENTAL DISORDERS

Many neuropsychiatric conditions are associated with mild-to-moderate olfactory dysfunction, and smell testing can be useful in several clinical situations. In the differential diagnosis of dementia, anosmia supports a diagnosis of Lewy body dementia or (if memory deficits predominate) alcohol amnestic disorder. If present or future Parkinson's disease is suspected, anosmia supports the diagnosis. Pathologically confirmed Lewy body dementia is strongly associated with anosmia.[14,15] It seems then that synucleinopathies (including Lewy body dementia) but not tauopathies (including Alzheimer's disease) are more marked by olfactory insensitivity.[16]

If olfactory acuity is intact (no anosmia), poor olfactory differential identification suggests current or developing Alzheimer's dementia. If olfactory acuity and identification are both intact, depressive pseudodementia or vascular dementia are more likely than Alzheimer's disease.

Parkinson's disease. Smell testing can be helpful in ruling in or out Parkinson's disease, particularly when associated features or response to dihydroxyphenylalanine (DOPA, precurser to dopamine and standard treatment for Parkinson's disease) raise doubts about the diagnosis. Depression and anosmia are common features of Parkinson's disease, and both can precede the usual motor manifestations. Thus, unexplained olfactory deficits in mid-life or later suggests a pre-motor phase of Parkinsonism,[16,17] especially if there are other Parkinson-related problems, such as executive dysfunction, rapid eye movement (REM) behavior (i.e., gross motor behavior during REM sleep, such as sleep walking), and depression. In the earliest phase of motor involvement, olfactory identification distinguished Parkinson's disease from healthy people more than any motor task,[18] so identification testing could help clarify ambiguous diagnoses. For example, in essential tremor (which can be difficult to distinguish from Parkinson's disease), olfactory identification was normal.[19] Supranuclear palsy, corticobasal degeneration, multiple systems atrophy, vascular Parkinsonism, and the new "Parkin" variant (mutation of the Parkin 2 gene) have normal or mildly impaired olfaction.[20,21] In Parkinson's disease proper (with motor manifestations), diminished olfactory acuity is the norm.[22]

TABLE 1. Summary of clinical implications of olfactory performance

DISORDER	ANOSMIA	MISIDENTIFICATION*	COMMENTS
LBD	Common	Common	Distinguishes LBD from Alzheimer's disease
Alcohol amnestic	Common	Common	Supports distinction from dementias
PD	Common	Common	Distinguishes PD from other Parkinsonian syndromes
TBI	Common (variable results)	Common	Can rule in TBI in certain situations
Down syndrome	Rare	Common	Disproportionate to cognitive disability
Congenital anosmia	Universal	Universal	Associated with other maldevelopment signs
Schizophrenia	Rare	Common	Anosmia suggests another diagnosis
Anxiety	Rare	Increased in PTSD	No important comments
Rhinitis/sinusitis	Common	Common	Temporary, sometimes chronic or permanent
Lesions of olfactory receptors or nerve	Common	Common	No important comments
Lesions of frontal or medial temporal lobe	Rare	Common	No important comments

*Note that identification deficits are always at least as common as acuity deficits (anosmia), because stimulus sensitivity is prerequisite for stimulus identification.
Key: LBD=Lewy body dementia; PD=Parkinson's disease; TBI=traumatic brain injury; PTSD=posttraumatic stress disorder.

NEUROANATOMIC CORRELATES OF OLFACTION DEFICITS: DEVELOPMENTAL ANOMALIES, SPHENOIDAL RIDGE TUMOR, EPILEPSY, BRAIN LESIONS, TRAUMATIC BRAIN INJURY

Some patients are born anosmic because of failure to develop brain olfactory structures, most notably Kallmann syndrome (with hypogonadotropic hypogonadism)[23] and the CHARGE syndrome.[24] These are rare conditions with numerous other signs of maldevelopment, so they are unlikely to explain newly discovered anosmia.

Anosmia can also point to problems in or near the olfactory nerve at the ventral frontal lobe. Unilateral anosmia with ipsilateral optic nerve atrophy and contralateral papilledema (Foster-Kennedy syndrome) suggest a sphenoidal ridge tumor. Olfactory identification deficits can be seen in epilepsy with a right temporal lobe focus,[25] temporal lobe lesions,[26] frontal lobe lesions,[27] and after frontal or temporal lobectomy.[28]

Traumatic brain injury (TBI). TBI is one of the most common neurologic causes of psychiatric syndromes. TBI is identified among possible risk factors for schizophrenia, posttraumatic stress disorder (PTSD), dementia, and others.[29] A history of TBI can be difficult to establish; psychiatric effects of TBI (post-concussive syndrome) overlap with many psychiatric conditions. Because it requires a relatively long and small axon bundle travelling close to bone, smell is unusually vulnerable to TBI. Results vary among studies, but the rate of anosmia may be 7 to 8 percent in TBI and four percent in mild TBI.[6,30]

PSYCHIATRIC DISORDERS ASSOCIATED WITH OLFACTORY SYMPTOMS

Schizophrenia. Olfactory identification deficits have been repeatedly found in schizophrenia, although acuity (detection threshold) seems to be unaffected.[31] Olfactory processing deficits may contribute to the neglect of personal hygiene seen commonly in schizophrenia.[32] Anosmia is uncommon (less than 1%) in

schizophrenia, but more common in certain conditions that can simulate schizophrenia (e.g., frontal lobe lesions, Lewy body dementia, alcohol amnestic disorder), so it can alert one to the likelihood of another illness

Alzheimer's disease. Alzheimer's patients do not tend to have total loss of olfaction (anosmia), but olfactory identification deficits effectively distinguish dementia (of the Alzheimer's type) from depression,[33–35] with sensitivity and specificity perhaps exceeding the mini-mental state examination.[34] In Alzheimer's disease, olfactory identification deficits present early, so they can predict future Alzheimer's dementia,[36–38] especially in those with the ApoE4 allele[36] and in those unaware of their olfactory deficits.[39] In dementia, olfactory dysfunction accurately distinguishes Alzheimer's disease from vascular dementia.[40]

PTSD. Patients with PTSD seem to have increased olfactory identification deficits,[41] but a possible role of TBI (common in many PTSD populations) was not addressed.

Mental retardation, attention deficit hyperactivity disorder (ADHD), and Down syndrome. Cognitive deficits are associated with olfactory identification deficits, much as they are associated with deficits in higher order processing of other sensory modalities. Olfactory identification deficits are prevalent in developmental disturbances of cognition, including mental retardation and attention deficit hyperactivity disorder.[42]

Down syndrome is associated with olfactory identification deficits (more than in other subjects matched for cognitive level), possibly reflecting the development of Alzheimer's pathology in adulthood.[43]

Human immunodeficiency virus (HIV) infection. HIV infection is associated with olfactory insensitivity regardless of stage or duration; identification deficits are related to cognitive decline.[44,45]

Alcohol amnestic disorder. Anosmia is usually found in alcohol amnestic disorder (Korsakoff psychosis) and distinguishes it from Alzheimer's dementia where there is an identification deficit but not anosmia.[6,46]

PSYCHIATRIC CONDITIONS NOT ASSOCIATED WITH OLFACTORY DEFICITS: MAJOR DEPRESSION, PANIC DISORDER

Major depression and panic disorder do not show consistent olfactory deficits. Seasonal depression may even bring with it super-normal sensitivity.[47] Olfactory identification deficits effectively distinguish dementia (of the Alzheimer's type) from depression,[33–35] with sensitivity and specificity perhaps exceeding the mini-mental state examination.[34]

TESTING OLFACTION

It might be quicker to ask the patient about loss of smell, but this is not reliable.[48] First one needs stimuli. Substances whose vapors cause mucosal irritation (alcohol, ammonia, peppermint, wintergreen) should be avoided, as even the anosmic patient may detect these stimuli via trigeminal afferents.[49] Suitable stimuli for research or specialty use are available for purchase (www.sensonics.com). In clinical practice, the usual stimuli are common food-stuffs that might be available in packets, such as coffee or chocolate.

Like any sense, we can test olfaction at several levels, from basic acuity to higher order processing, memory, and many types of responses. We can assess acuity by determining a threshold, or the minimum stimulus strength required for the individual to detect an odor. Threshold testing requires exacting preparation of stimuli in various strengths (concentrations). Bottles containing odorants in solution at a range of concentrations are often used. Clinically, clinicians are interested in detecting very low acuity (very high threshold), otherwise known as anosmia.

Olfactory identification, in which the patient names an odor, is frequently used in psychiatric research. The patient is presented with a common smell for up to five seconds and asked to identify the smell. To correctly identify the odor, the patient must be able to detect it, recognize it, and produce a relevant word for it. Probably because many odor names are not in every day use, many healthy people will be unable to name a given smell, but do much better in a multiple choice format. Another task, similar but less dependent on verbal ability, is to distinguish among odors.

Olfactory acuity and identification have distinct implications, although they are often tested together and are of course strongly correlated.[5,6] Anosmia represents a problem with the olfactory receptors or olfactory nerve (sometimes the problem is that the stimulus cannot reach the receptor). Anosmia can be inferred from olfactory identification performance (approximately chance performance). Normal acuity is necessary, but not sufficient for accurate olfactory identification. Whether by freely naming odors, selecting from among names, or discriminating among odors, olfactory identification tasks reflect higher order processing.

Olfactory screening for anosmia usually requires nothing more than presenting one or two common and nonirritating stimuli. If the patient cannot identify one, four possible choices should be provided. If the patient cannot identify the odor or denies smelling anything, a second stimulus should be presented in the same fashion. This allows one to inquire whether the two stimuli are the same or different. Further investigation may be warranted if the patient cannot identify either odor. If the patient cannot identify either stimulus and cannot distinguish between them, it is likely that the patient is anosmic. If the patient cannot distinguish a third odor from a blank (no stimulus), anosmia is virtually established. Those failing to identify even one of three stimuli are three times more likely to have anosmia.[50]

The enthusiast can purchase one of the olfactory identification test kits, such as the highly validated University of Pennsylvania Smell Identification Test,[6] or the well-validated and more

economical "Sniffin' Sticks."[5] Briefer screening instruments are also available.[33,51,52] Another kit, the Early Alert Alzheimer's Screening Test,[53] is a brief identification test marketed directly to consumers as a screening test for dementia (the concept is much criticized on several grounds). Although these tests focus on identifying odors, they can also be used to detect anosmia (when identification performance is around chance) and malingered deficits (when performance is below chance).[6] Another approach to anosmia testing is the "sniff magnitude test,"[54] which is based on reflexive sniffing rather than verbal response. Other specialty olfactory tests include olfactory memory and the appreciation of positive and negative odors.[55,56]

FURTHER EVALUATION OF ANOSMIA

Anosmia is an important finding. If there are no obvious explanations (such as current sinusitis or rhinitis), further ear, nose, and throat consult will usually be indicated, if only for further olfactory testing. Brain imaging is worthwhile to rule out structural causes. Even when there is a history of upper respiratory infection or head injury coinciding with the loss of smell, the evaluation of persisting anosmia should at a minimum include inquiring into changes in personality and occupational performance, screening memory and extrapyramidal motor function, and neuroimaging. Neuropsychological assessment should also be considered.

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